AF/1632 #2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the Application of:	
Ralph R. WEICHSELBAUM *et al.*	Appeal No.: Attorney Docket
	UCT-105.0 US
Serial No.: 08/289,290	(8798/88589)
Filed: August 11, 1994	Group Art Unit 1632
For CONSTITUTIVE GENE EXPRESSION IN CONJUNCTION WITH IONIZING RADIATION	
Examiner: Q. J. Li	

APPELLANTS' SECOND CORRECTED BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner of Patents
P.O. Box 1450
Alexandria , VA 22313-1450

Sir:

This is Applicants' Second Corrected Brief on Appeal filed in response to a Notification of Non-Compliance of the previously filed Brief on Appeal. That previously filed Brief on Appeal was an appeal from the Final Office Action dated July 3, 2003, finally rejecting several claims. A Petition for a one-month extension of time for the filing of that Brief and the required fee were enclosed.

REAL PARTY IN INTEREST

The patent application that is the subject of this appeal is assigned to ARCH Development Corporation and Dana-Farber Cancer Institute and is exclusively licensed to GenVec, Inc.

RELATED APPEALS AND INTERFERENCES

The patent application that is subject to this appeal was previously the subject of Appeal No. 1999-1365, on which a decision was rendered on Applicants' behalf by the Board of Patent Appeals and Interferences on March 14, 2002.

STATUS OF THE CLAIMS

Claims 1-3, 6, 8-14, 18-22, 26-29, and 31-42 are currently pending. The Notice of Appeal filed on May 30, 2003 indicated claims 29, 31-34, and 37-40 as being the subject of this appeal. Claims 1-3, 6, 8-14, 18-22, 26-28, 31-36, 41, and 42 were deemed allowable in the Advisory Action of May 5, 2003. Original claims 4, 5, 7, 15, 16, and 23-25 were cancelled in an Amendment filed December 12, 1997. Original claims 17 and 30 were cancelled in an Amendment filed on November 7, 2002.

There was some question about the allowance of claims 31-34 in the Advisory Action, but, in a telephonic interview on July 2, 2003, Supervisory Patent Examiner Deborah Reynolds confirmed the allowability of claims 31-34 and also indicated that claim 38 and claim 39 were allowable.

Thus, claims 29, 37, and 40 are the only claims subject to this appeal. All of the pending claims are set forth in the Appendix attached hereto.

STATUS OF THE AMENDMENTS

An Amendment After Final was filed on March 28, 2003, which amended claims 29 and 40. This Amendment was not entered. See, Advisory Action dated May 9, 2003. The amendments submitted have therefore not been accepted.

SUMMARY OF THE INVENTION

The invention defined by rejected claims 29 and 37 is directed to a pharmaceutical composition comprising a genetic construct containing a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter, which is dispersed in a pharmacologically acceptable carrier. The genetic construct is packaged within an adenovirus particle, which can contain a deletion of the E1 region and/or the E3 region of the adenoviral genome (see, e.g., page 11, lines 11-26, page 18, lines 9-12, and page 23, lines 22-25). The invention defined by claim 40 is directed to a process of inhibiting growth of a tumor in a host comprising (a) injecting into the tumor a therapeutically effective amount of the pharmaceutical composition defined by claim 29 and (b) administering to the host a dose of ionizing radiation between 50 and 70 Gray, whereby the growth of the tumor is inhibited by expression of the nucleic acid encoding a TNF-α and the

administration of ionizing radiation (see, e.g., page 42, line 8, through page 45, line 10).

ISSUES

(A) Whether the invention defined by claims 29 and 37 is anticipated by the disclosures of U.S. Patent 5,935,935 (Connelly et al.).

(B) Whether the invention defined by claim 29 is anticipated by the disclosures of U.S. Patent 6,228,356 (Glorioso et al.).

(C) Whether the invention defined by claims 29 and 37 is obvious over the disclosures of U.S. Patent 6,143,290 (Zhang et al.) in view of Walther et al., *Anticancer Res.*, *13*, 1565-74 (1993).

(D) Whether the invention defined by claim 40 complies with the written description requirement.

GROUPING OF CLAIMS

The rejected claims do not stand or fall together. Each of the three rejected claims stands on its own merits, and, therefore, the rejected claims can be categorized into three groups. Group I consists of claim 29, Group II consists of claim 37, and Group III consists of claim 40.

Each of these claims is the subject of different rejections or combinations of rejections. The claims of Group I and Group II are subject to prior art rejections. The claim of Group III is subject to a written description rejection. Thus, if the rejections of the claims of Group I or Group II were

upheld, such rejections would have no effect on the patentability of the claim of group III (i.e., claim 40). Moreover, a prior art disclosure that anticipates or renders obvious the subject matter of the claim of Group I would not necessarily anticipate or render obvious the claim of Group II, which further limits the pharmaceutical composition of claim 29. This is evidenced by the rejection of claim 29, and not claim 37, under Section 102(e) in view of U.S. Patent 6,228,356. As such, the claims of the present application do not stand or fall together.

ARGUMENT

(A) Rejection Of Claims 29 And 37 Under 35 U.S.C. §102(e) In View Of U.S. Patent 5,935,935 (Connelly et al.) Was Improper

The final Office Action dated January 30, 2003, contended that the Connelly et al. (Connelly) patent anticipates claims 29 and 37 by allegedly disclosing a genetic construct (e.g., an adenoviral vector) that encodes a therapeutic agent (e.g., TNF-α). The Action further alleged that, when the genetic construct is an adenoviral vector, the Connelly patent discloses that the adenoviral vector is deficient in the E1 and E3 regions, is packaged in an infectious viral particle, and is administered in combination with a pharmaceutically acceptable carrier to a patient.

Contrary to the assertion of the Action, the Connelly patent does not anticipate the invention defined by claims 29 and 37. In this respect, the Connelly patent discloses several

therapeutic genes, besides TNF-α, that are suitable for administration to a host, including Factor VIII, Factor IX, cytokines, interferons, interleukins, GM-CSF, adenosine deaminase, lypmohpkines, CFTR, insulin, and other therapeutic genes (see col. 11, lines 29-53). The Connelly patent also discloses several promoters, both constitutive and inducible, suitable for controlling expression of the therapeutic gene, including adenoviral promoters, the CMV promoter, the RSV promoter, the mouse mammary tumor virus (MMTV) promoter, heat shock promoters, the metallothionein promoter, and other promoters (see col. 7, lines 20-34).

The Connelly patent, however, does not disclose a pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle, as required by claims 29 and 37. Accordingly, the section 102(e) rejection is improper and should be reversed. In addition, that patent also does not provide any signposts that point the skilled worker specifically to a claimed composition, so the subject matter of claims 29 and 37 is also not obvious in view of those disclosures.

(B) Rejection Of Claim 29 Under 35 U.S.C. §102(e) In View Of U.S. Patent 6,228,356 (Glorioso et al.) Was Improper

According to the final Office Action, the Glorioso et al. (Glorioso) patent anticipates claim 29 by allegedly

disclosing recombinant viral vectors (e.g., adenovirus vectors) that encode a cytokine (e.g., TNF-α), and that are administered to a host in combination with a pharmaceutical carrier. It is noted that, like the Connelly patent discussed above, the Glorioso patent discloses several vectors (e.g., retrovirus, adenovirus, adeno-associated virus, etc.) and several genes (e.g., cytokines, proteinase inhibitors, an IL-1 receptor antagonist, etc.) that are suitable for administration to a host. With respect to promoters, the Glorioso patent discloses the use of a CMV promoter or a retroviral promoter only in the context of regulating expression of an interleukin-1 gene.

The Glorioso patent also does not disclose a pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle, as required by claim 29. Accordingly, the section 102(e) rejection is improper and should be reversed. In addition, as with the Connelly patent above, the Glorioso disclosures also provide no sign posts that lead a skilled worker specifically to the claimed subject matter, and so claim 29 is also not obvious in view of the disclosures of Glorioso.

(C) Rejection Of Claims 29 And 37 Under 35 U.S.C. § 103(a) Over The Disclosures Of U.S. Patent 6,143,290 (Zhang et al.) In View Of The Disclosures Of Walther et al., *Anticancer Res.*, *13*: 1565-74 (1993) Was Improper

The final Office Action contended that the invention defined by claims 29 and 37 would have been obvious to one of ordinary skill in the art in view of the combination of the teachings of the Zhang et al. patent and those of the Walther paper. The Zhang et al. (Zhang) patent discloses an E1/E3-deficient adenovirus construct encoding a p53 coding sequence, the expression of which can be regulated by the CMV promoter or SV40 promoter. The Zhang patent discloses that a "rapid decrease" in p53 gene expression was observed using the adenoviral vector disclosed therein (see, e.g., column 14, lines 30-35). The Walther paper discloses the introduction of a retroviral vector encoding the TNF-α gene to tumor cells, which is associated with constitutive TNF-α expression and tumor growth inhibition.

Thus, in order to arrive at the invention defined by claims 29 and 37 based on the disclosure of the Zhang patent and the Walther paper, one of ordinary skill in the art would have to (a) ignore the Zhang patent teaching of decreased p53 expression observed using the adenoviral vector disclosed therein, (b) ignore the Walther paper's teaching of tumor growth inhibition associated with constitutive expression of retrovirally-encoded TNF-α, and (c) instead construct an adenoviral vector encoding the TNF-α gene under the control of a constitutive promoter. It is submitted that the final Office

Action does not provide any basis for one of ordinary skill in the art to modify the disclosure of the Zhang patent and the Walther paper in the significant manner required to arrive at the present invention, except perhaps after reading the present disclosure and using hind sight. Therefore, the Section 103 rejection of claims 29 and 37 is improper and should be reversed.

(D) Rejection Of Claim 40 Under 35 U.S.C. § 112, First Paragraph

The Action contended that claim 40 lacks sufficient written description in that the specification does not specify a dose of radiation between 50 and 70 gray as set forth in claim 40. Specifically, the Action alleged that the specification only discloses a dose of radiation between 5 and 20 gray (see final Office Action dated January 30, 2003 at pages 2 and 3, bridging paragraph). Contrary to that contention, Example VI of the present application discloses that "[t]umors will be irradiated on five succeeding days, generally Monday through Friday, at 2 Gy/day to a total dose of **50 to 70 Gy**" (see page 42, lines 19-21, emphasis added). Thus, the subject matter of claim 40 is adequately described in the specification to convey to one of ordinary skill in the art that Applicants had possession of the invention.

With respect to the alleged new matter introduced by claim 40, it is submitted that the language used in claim 40 conveys the meaning of the disclosure to the worker of ordinary skill in a manner close enough to the precise language of the specification so as to not add new matter. As the Board and

Court have said in several cases, the claim language need not mirror the language of the specification *in ipsis verbis* [In re Wright, 9 USPQ2d 1649 (CAFC 1989) and Freerdson v. Gass, 21 USPQ2d 2007 (BdPatApp &Int 1990)]. Examination of the claim in the attached appendix and comparison of that language to the language at page 42, lines 19-21, a true copy of which is attached as Exhibit A hereto, will show that no new matter has been added and that this basis for rejection should be withdrawn. Accordingly, the Section 112, first paragraph, rejection is improper, and should be reversed.

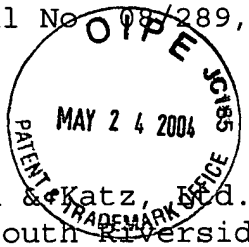
Three copies of this Appellant's Brief on Appeal are enclosed.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be a required petition.

Respectfully submitted,

By _____
Edward P. Gamson, Reg. No. 29,381

Enclosures
Appendix I (Claims in the case)
Exhibits A



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CERTIFICATE OF MAILING

I hereby certify that this Appellant's Brief on Appeal, in triplicate, its fee, Appendix and Exhibits are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on May 20, 2004.

Edward P. Gamson

APPENDIX

1. A process of treating a human cancer patient comprising providing to a cancer cell in said patient a nucleic acid encoding a radiosensitizing polypeptide operatively linked to a constitutive promoter and contacting said cell with ionizing radiation, whereby the nucleic acid is expressed to produce the radiosensitizing polypeptide and the cancer is treated.

2. The process of claim 1, wherein the nucleic acid encodes a TNF-α.

3. The process of claim 18, wherein the radioprotecting factor is MnSOD, IL-1 or IL-2.

6. The process of claim 1, wherein the constitutive promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin of replication, the β-actin promoter, or the Egr enhancer/promoter.

8. The process of claim 1, wherein said nucleic acid is provided by transfection by liposomes, adenovirus or HSV-1.

9. The process of claim 8, wherein the liposome comprises DOTMA, DOTMA/DOPE, or DORIE.

10. The process of claim 8, wherein the transfection is by adenovirus infection.

11. The process of claim 8, wherein the transfection is by HSV-1 infection.

12. A process of sensitizing a cell to the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a nucleic acid that encodes a cytokine, wherein said cytokine is synthesized in and secreted from said cell.

13. The process of claim 12, wherein the nucleic acid that encodes the cytokine is positioned under control of a promoter other than an adenovirus promoter.

14. The process of claim 13, wherein the promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer-promoter, the SV40 early promoter, the SV40 late enhancer/promoter, the MMSV LTR, the SFFV enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

18. A process of radioprotecting a cell from the effects of ionizing radiation comprising:

(a) obtaining a genetic construct comprising a nucleic acid encoding a cell radioprotecting factor operatively linked to a constitutive promoter; and

(b) transfecting a cell with the genetic construct; whereby said radioprotecting factor is expressed and said cell is protected from said effects.

19. The process of claim 18, wherein the transfecting is by liposomes, adenovirus, or HSV-1.

20. The process of claim 19, wherein the liposome comprises DOTMA, DOTMA/DOPE, or DORIE.

21. The process of claim 19, wherein the transfection is by adenovirus infection.

22. The process of claim 19, wherein the transfection is by HSV-1 infection.

26. A process of radioprotecting a cell from the effects of ionizing radiation comprising transfecting the cell with an adenovirus vector construct comprising a nucleic acid encoding a radioprotecting factor in a mammalian cell.

27. The process of claim 26, wherein the nucleic acid is positioned under control of a promoter other than an adenovirus promoter.

28. The process of claim 27, wherein the promoter is the immediate-early CMV enhancer/promoter, the RSV enhancer/promoter, the SV40 early promoter, the SV40 late

enhancer/promoter, the MMSV LTR, the SFFVs enhancer/promoter, the EBV origin of replication, the β-actin promoter or the Egr enhancer/promoter.

29. A pharmaceutical composition comprising a genetic construct comprising a nucleic acid that encodes a TNF-α operatively linked to a constitutive promoter dispersed in a pharmacologically acceptable carrier, wherein the genetic construct is packaged within an adenovirus particle.

31. A method of expressing a radioprotecting or radiosensitizing factor in a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 29.

32. The method of claim 31, wherein the administering is by means of an intravenous injection of from 10^8 to 10^{11} virus particles.

33. The method of claim 31, wherein the mammal is a mouse.

34. The method of claim 31, wherein the mammal is a human.

35. A process of inhibiting growth of a tumor comprising the steps of:

(a) delivering to said tumor a therapeutically effective amount of a DNA molecule comprising a constitutive promoter operatively linked to a region encoding a polypeptide having the ability to inhibit growth of a tumor cell, which coding region further is operatively linked to a transcription-terminating region, whereby said polypeptide is expressed; and

(b) exposing said cell to an effective dose of ionizing radiation, whereby the growth of said tumor is inhibited by said polypeptide and ionizing radiation.

36. A method of assessing the response of a cell to the constitutive production of radiosensitizing or radioprotecting factors following ionizing radiation comprising:

(a) growing the cell in culture;

(b) transfecting the cell with a genetic construct comprising a nucleic acid that encodes the cell radiosensitizing factor or radioprotecting factor operatively linked to a constitutive promoter, whereby said nucleic acid is expressed to produce the radiosensitizing factor or radioprotecting factor;

(c) exposing the cell to an effective dose of ionizing radiation; and

(d) assessing the response of the cell.

37. The pharmaceutical composition of claim 29, wherein the adenovirus particle contains a deletion of the E1 region and/or the E3 region of the adenoviral genome.

38. A process of inhibiting growth of a tumor in a host comprising the steps of:

(a) injecting into the tumor a therapeutically effective amount of the pharmaceutical composition of claim 29, and

(b) administering to the host an effective dose of ionizing radiation, whereby the growth of the tumor is inhibited

by expression of the nucleic acid encoding a TNF-α and the administration of ionizing radiation.

39. The process of claim 38, wherein the amount of the pharmaceutical composition is between 10^8 and 10^{11} plaque forming units.

40. The process of claim 38, wherein the dose of ionizing radiation is between 50 and 70 Gray.

41. The process of claim 35, wherein the polypeptide is a TNF-α.

42. The process of claim 12, wherein the cytokine is a TNF-α.

and addition of complete medium. The cells were then incubated as above until harvest. 60mm culture dishes and a final volume of 2ml per dish were used for all transfections. Cells maintained in culture longer than 24 hours underwent a daily medium change.

EXAMPLE VI

Protocol for Phase I clinical Trial Combining Adenovirus type 5

Patients with incurable, recurrent, head and neck primaries that are not amenable to surgery will be eligible for this study.

A dose escalation of Adenovirus type 5 (Ad5) containing the Egr-TNF genetic construct will be injected into the tumor at 10^8 to 10^{11} plaque forming units (PFU) per tumor using 2 injection sites and a 25 gauge 1.5 inch needle. Tumors will be injected each week on Mondays for 5 to 7 consecutive weeks.

Tumors will be irradiated on five succeeding days, generally Monday through Friday, at 2 Gy/day to a total dose of 50 to 70 Gy.

Evaluation of Response to Treatment

Patients will be evaluated on the basis of history/physical exam, vital signs, performance status, height/weight/BSA, CBC/Diff/Platelets, SMA-17, PT/PTT, CXR, EKG, serum TNF, and tumor measurements. Parameters will be measured during prestudy, at one week, and at the end of the study. Tumor measurements will be obtained when available by an appropriate study (x-rays, scans, tumor markers, etc.) during the prestudy period and within 2 to 4 weeks of completion of study.